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Causal role of immune cells in obstructive sleep apnea hypopnea syndrome: Mendelian randomization study

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Abstract

BACKGROUND

Despite being one of the most prevalent sleep disorders, obstructive sleep apnea hypoventilation syndrome (OSAHS) has limited information on its immunologic foundation. The immunological underpinnings of certain major psychiatric diseases have been uncovered in recent years thanks to the extensive use of genome-wide association studies (GWAS) and genotyping techniques using high-density genetic markers (*e.g.*, SNP or CNVs). But this tactic hasn't yet been applied to OSAHS. Using a Mendelian randomization analysis, we analyzed the causal link between immune cells and the illness in order to comprehend the immunological bases of OSAHS.

AIM

To investigate the immune cells' association with OSAHS *via* genetic methods, guiding future clinical research.

METHODS

A comprehensive two-sample mendelian randomization study was conducted to investigate the causal relationship between immune cell characteristics and OSAHS. Summary statistics for each immune cell feature were obtained from the GWAS catalog. Information on 731 immune cell properties, such as morphologic parameters, median fluorescence intensity, absolute cellular, and relative cellular, was compiled using publicly available genetic databases. The results' robustness, heterogeneity, and horizontal pleiotropy were confirmed using extensive sensitivity examination.

RESULTS

Following false discovery rate (FDR) correction, no statistically significant effect of OSAHS on immunophenotypes was observed. However, two lymphocyte subsets were found to have a significant association with the risk of OSAHS: Basophil %CD33dim HLA DR- CD66b- (OR = 1.03, 95%CI = 1.01-1.03, $P < 0.001$); CD38 on IgD+ CD24- B cell (OR = 1.04, 95%CI = 1.02-1.04, $P = 0.019$).

CONCLUSION

This study shows a strong link between immune cells and OSAHS through a gene approach, thus offering direction for potential future medical research.

Key Words: Obstructive sleep apnea hypopnea syndrome; Immunity; Causal inference; MR analysis; Sensitivity

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Core Tip: Our comprehensive bidirectional mendelian randomization analysis has revealed causal links between various immunophenotypes and obstructive sleep apnea-hypopnea syndrome (OSAHS), shedding light on the intricate web of relationships between OSAHS and the immune system.

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INTRODUCTION

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is characterized by an apnea-hypopnea index of 5 or more, accompanied by symptoms such as excessive daytime somnolence, two or more episodes of asphyxia, wheezing, frequent arousals, daily weariness, lack of attention, or memory loss[1,2]. Research has illustrated that intermittent hypoxia and hypopnea can elevate the diastolic function of respiratory muscles, activate the sympathetic nervous system, induce an oxidative stress response, worsen vascular endothelial damage, and ultimately lead to atherosclerosis and recurrent apnea[3,4]. Emphasizing the value of early treatment for OSAHS is crucial. Systemic inflammation, cognitive decline, cardiovascular and metabolic problems, and delayed or neglected therapy might all arise[5,6].

Current research is exploring the complicated relationships between OSAHS and the immune system, particularly focusing on how inflammatory factors impact immune cell involvement. Studies have revealed that patients with moderate-to-severe OSAHS show significantly lower natural killer cell percentages and immunoglobulin M levels, alongside notably elevated levels of interleukin (IL)-4, IL-13, C-C motif chemokine (CCL)-11, CCL-24 (a type 2 immune-associated marker), IL-17A (a type 3 immune-associated marker)[7], and serum complement C3 levels[8]. These findings suggest that immune cells and inflammation may influence the development and symptoms of OSAHS. Additionally, genome-wide association studies are crucial for understanding the link between the disease and the immune system by examining genetic variations in large cohorts. Recent investigations suggest that signal variants in the COX20, PTPDC1, and TMOD4 genes may be linked to the OSAHS phenotype in affected families[9]. Therefore, it is anticipated that identifying gene loci and networks using genome-wide association studies (GWAS) will enhance our understanding of the complex interplay among genetics, immune response, and disease, ultimately guiding personalized treatment strategies for OSAHS[10].

Mendelian randomization (MR) functions as a statistical method primarily utilized for inferring epidemiological causality by leveraging Mendelian genetic principles[11]. Preserving the logical sequence of causality is crucial in the Mendelian randomization approach[12]. The results of previous observers have confirmed a specific link between immune cell characteristics and OSAHS, thus reinforcing the assumption that there is a correlation between the two[13,14]. This study used a two-sample magnetic resonance integrated method to investigate the causal association of immune cell characteristics with OSAHS.

MATERIALS AND METHODS

Study design

We investigated the causal relationship of the 731 immune cell profiles with OSAHS by two-sample MR analysis. MR requires the use of genetic variation as a proxy variable for risk variation to satisfy three critical hypotheses in causal inferences: That (1) the exposure is expected to be directly correlated with the genetic variance; (2) as potential confounders, no genetic link is present between the exposure and the outcome; and (3) no genetic influence on the objective is exerted by channels independent of the exposure (Figure 1). The Institutional Review Board approved our study, and informed

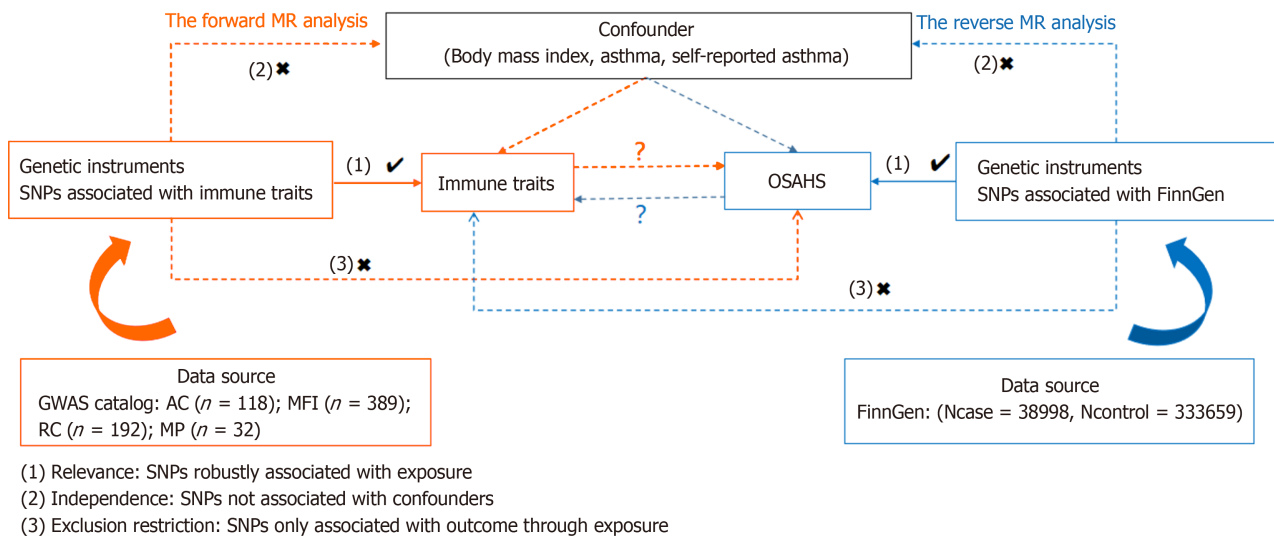


Figure 1 Overview of this bidirectional mendelian randomization study design. AC: Absolute cell count; MR: Mendelian randomization; SNPs: Single nucleotide polymorphisms; OSAHS: Obstructive sleep apnea hypoventilation syndrome; GWAS: Genome-wide association studies; RC: Relative cell count; MP: Morphologic parameters.

consent was obtained from the participants.

Sources of immune cross-genomic data

Comprehensive summary statistical data (ranging from accession numbers GCST0001391 to GCST0002121) containing all immunization profiles in the GWAS catalog are readily available[15]. This Genomic Study involved 3757 non-overlapping Europeans analyzed using high-density arrays based on the Sardinian Sequence Reference Panel[16]. The dataset comprised approximately 22 million SNP, which underwent correlation testing while adjusting for covariates like age, age 2, and sex. Among the 731 immunophenotypes identified, these include morphologic parameters (MP) (32), relative cell count (RC) (192), absolute cell count (AC) (118), and median fluorescence intensity (MFI), indicating the level of surface antigens (389). The MP features include CDC and TBNK panels. Meanwhile, the MFI, RC, and AC features cover a variety of immune cells such as B cells, myeloid cells, T cell maturation stage, TBNK, CDC, and monocytes (B cells, T cells, and natural killer proteins).

OSAHS genome-wide association study data sources

FinnGen provided the genome-wide association study (GWAS) summary statistics for OSAHS (<https://www.finnngen.fi/en>). 372657 European people were included in the research (Ncase = 38998, Ncontrol = 333659) for a GWAS. The GWAS identified over 16 million independent single nucleotide polymorphisms (SNPs).

Selection of instrumental variables

An instrumental variable (IV) extracted from version v1.90 was used to modify SNPs using a distance of 500 kb with a chain disequilibrium (LD) r^2 threshold of less than 0.1[17]. Calculation of LD r^2 used the 1000 Genomes Project as a reference panel, and the revised OSAHS significance threshold was established at 5×10^{-8} . The F statistic was calculated to evaluate the IV's strength and mitigate potential weak instrumental bias. The IV length for immunophenotyping ranged from 3 to 1641, with an average explanation of 0.021% (range 0.023% to 5.29%) for the associated immune characteristics.

Statistical analysis

All studies were analyzed using R version 4.3.1 software (<http://www.Rproject.org>). In particular, to explore the causal links between the 731 immunophenotypes and OSAHS, a set of analyses were performed using the "Mendelian Randomization" software (version 0.4.3)[18], including median-based weighted analysis[19], pattern-based weighted analysis[20], and inverse variance weighted (IVW) analysis[21]. Instrumental heterogeneity across variables was examined based on Cochran's Q statistic and P value (IV), supported with MR-Egger test, which identifies cross-sectional multidimensionality through a significant intercept term[22]. In addition, the analysis included using the MR-PRESSO software package to identify and exclude horizontal multidimensional entropy outliers that could significantly impact the estimation results [23]. After eliminating these SNPs, the IVW analysis was rerun. Additionally, SNPs potentially associated with those risk variables were tracked at the Phenoscanner V2 (<http://www.phenoscanner.medschl.cam.ac.uk/>) Web site ($P < 10^{-5}$). Finally, the analysis combines a funnel plot and a scatterplot, where the scatterplot reveals that outliers have the least significant effect on the data. In contrast, the funnel plots showed solid associations and a lack of heterogeneity.

RESULTS

Investigating the causal relationship between immunophenotypes and OSAHS

Using false discovery rate (FDR) correlation ($P_{\text{FDR}} < 0.05$), we identified two protective immunophenotypes against OSAHS: Basophil %CD33dim HLA DR- CD66b- and CD38 on IgD+ CD24- B cell. In particular, the ratio of basophil %CD33dim HLA DR- CD66b- to the risk of OSAHS was 1.03 (95%CI = 1.01-1.03, $P_{\text{FDR}} = 0.04$, $P = 0.256$, [Supplementary Table 1](#)) as measured by the IVW method. Four other methods also gave similar results: the weighted median method (OR = 1.03, 95%CI = 1.01-1.03, $P = 0.009$), the simple mode method (OR = 1.05, 95%CI = 1.00-1.05, $P = 0.053$); the weighted mode method (OR = 1.03, 95%CI = 1.01-1.03, $P = 0.026$), and MR-Egger method (OR = 1.02, 95%CI = 0.99-1.06, $P = 0.256$). By applying the IVW technique, the OR of CD38 on IgD+ CD24- B cell on OSAHS risk was calculated to be 0.064 (95%CI = 0.89-0.96, $P_{\text{FDR}} = 0.04$, $P < 0.001$, [Supplementary Table 1](#)). The results were similar for weighted mode (OR = 1.03, 95%CI = 1.00-1.03, $P = 0.066$); weighted median (OR = 1.04, 95%CI = 1.01-1.04, $P = 0.019$); Simple mode (OR = 1.03, 95%CI = 0.99-1.03, $P = 0.208$); and MR-Egger (OR = 1.05, 95%CI = 1.01-1.05, $P = 0.015$). Furthermore, the MR-Egger intercept and MR-PRESSO global tests for both associations dismissed the possibility of horizontally collapsed effects. Sensitivity analyses furnished detailed information that affirmed the robustness of the identified causal relationships ([Figure 2](#) and [Supplementary Table 2](#)). The resilience of the data was further illustrated through funnel scatterplots ([Supplementary Figure 1A](#) and [Supplementary Figure 2A](#)) and plots ([Supplementary Figure 1B](#) and [Supplementary Figure 2B](#)).

Examination of the causal relation of OSAHS onset on immunophenotypes

In exploring the causal effect of OSAHS on immunophenotypes, we used the IVW approach as the primary analytical method for the two-sample MR analysis. Although adjusted for multiplicity of tests using the FDR method, we did not identify any immunologic features at the 0.05 significance level. However, when loosely thresholding the FDR, we identified 37 cellular phenotypes with an FDR of 0.56, with the highest expression of receptor proteins in B-cell subpopulations, such as BAFF-R on IgD+ CD24 - (OR=1.13, 95%CI = 1.03-1.23, $P = 0.006$); BAFF-R on IgD+ CD38br (OR = 1.11, 95%CI = 1.02-1.03, $P = 0.026$); BAFF-R on IgD+ CD38dim (OR = 1.11, 95%CI = 1.02-1.21, $P = 0.019$). Other cellular subpopulations also had high CD19 expression, such as CD19 on IgD+ CD38- unsw mem (OR = 1.17, 95%CI = 1.03-1.31, $P = 0.009$), CD19 on IgD+ CD24+ (OR = 1.11, 95%CI = 1.02-1.21, $P = 0.014$), and other phenotypes, such as resting Treg AC, EM CD8br %T cells. Monocytes AC, B cells % CD3- lymphocytes, *etc.* ([Supplementary file 3](#)).

DISCUSSION

We explored the causal link between 731 immune cell characteristics and OSAHS by leveraging an extensive dataset of publicly available genetic information. This remains the sole MR investigation delving into the causal relationship between numerous resistant phenotypes and OSAHS. The research encompassed four categories of immune traits (MFI, RC, AC, and MP). Within these categories, two immunophenotypes demonstrated a substantial causal impact on OSAHS ($P_{\text{FDR}} < 0.05$) ([Figure 3](#)).

Our studies have shown that the risk of developing OSAHS increases with the percentage of CD38 in IgD+ CD24-B cells. Altered CD38 expression or increased function of the cyclic ADP ribozyme associated with CD38 in this cell subset has been directly linked to the treatment of a variety of diseases, including cancer, asthma, and neuroimmune diseases [24]. It has been shown that CD38 plays a role in calcium regulation in airway smooth muscle (ASM) and that upregulation of CD38 levels improves Ca^{2+} responses when airway smooth muscle is exposed to contractile agonists[25,26]. Experimental studies have also shown that CD38 increases airway inflammation and responsiveness by modulating intracellular calcium levels in mouse smooth muscle contractile (ASM) cells. Through a mechanism that is not dependent on CD38, bronchodilators are often used for clinical guidance in the medical management of chronic airway disease[27]. Additionally, in CRS patients with nasal polyps, elevated IgD CSR in mucosa-associated lymphocyte B-cell populations activates mast cells and may promote IgE production and eosinophilic inflammation[28]. Although the exact relationships between these variables are yet unknown, they all have an indirect impact on how OSAHS develops.

Plenty of studies have been done on the connection between basophils and airway inflammation. It has been demonstrated that basophil-associated OX40 ligand plays a key role in the onset of the Th2 response during airway inflammation[29], while basophil IL-4 is essential to the generation of NH-derived cytokines and chemokines, which in turn results in proteolytic allergen-induced airway inflammation. On the other hand, HLA-DR, or the human lymphocyte antigen D-related antigen, has been linked to immunological abnormalities and has been demonstrated to be significant in a number of autoimmune and neurological illnesses[30]. *HLA-DR* gene variations, for instance, have been linked to an increased risk of developing certain neuropsychiatric disorders. For instance, populations with severe depressive disorders, sleep disorders, and autistic spectrum disorders have been shown to express HLA-DRB1 at the HLA-DR regional locus at greater levels[31]. The results of this study also show that HLA-DR is strongly related to immunological abnormalities in patients with OSAHS[32]. Of particular interest is the aberrantly elevated levels of CD3- + HLA-DR cells in the peripheral blood of patients with sleep disorders[33]. These findings imply that immunological problems linked to sleep disorders and OSAHS include basophil% and HLA DR-CD66b-mediated cell subpopulations.

This study utilized a two-sample Mendelian randomization method, and the data were obtained from a sizable genomic study cohort containing 372657 individuals, ensuring robust statistical efficiency. Conclusions were based on genetic instrumental variables, and causal inferences employed diverse and powerful Mendelian randomization analysis techniques resistant to horizontal pleiotropy and other confounding variables. However, acknowledging several limitations is necessary. Firstly, despite numerous sensitivity analyses, a thorough assessment of horizontal pleiotropy

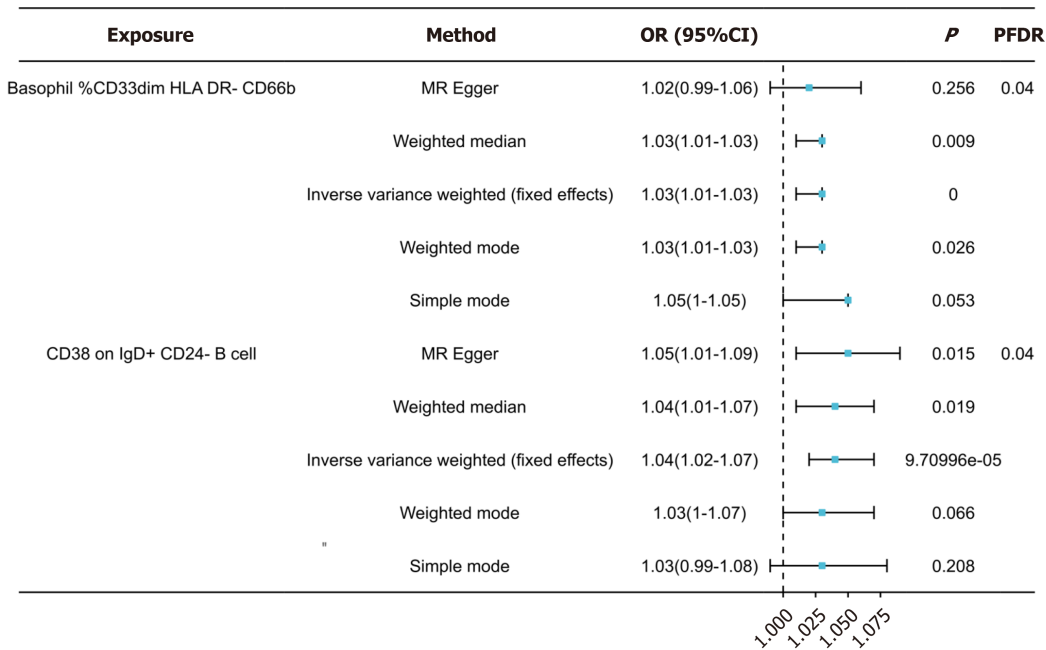


Figure 2 Forest plots showed the causal associations between immune cell traits and obstructive sleep apnea hypoventilation syndrome by using different methods.

Respiratory sleep apnea

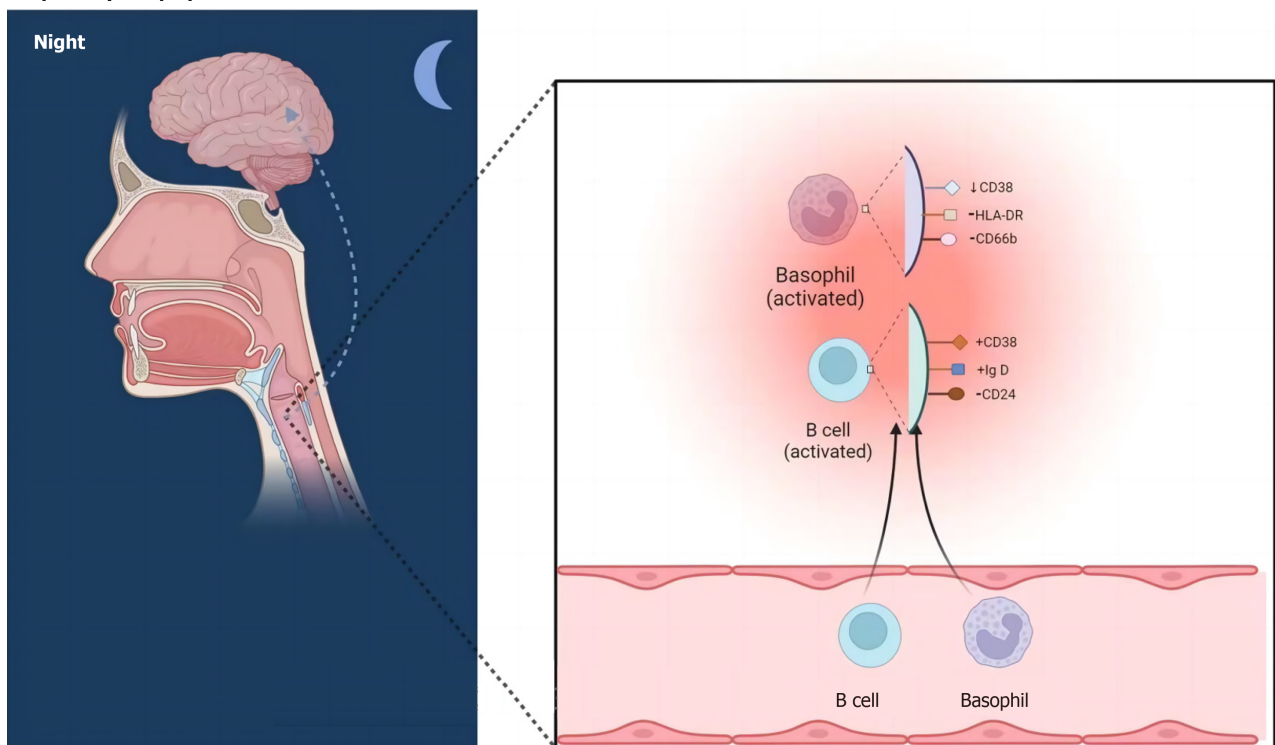


Figure 3 A diagram illustrates both cell subpopulations in the airways of patients with obstructive sleep apnea-hypopnea syndrome that are involved in inflammation.

remains challenging. Secondly, the lack of individual-level data could have helped stratified population analyses. Thirdly, the dependence of European databases restricts the generalization of the findings across other races. Finally, the adjustable result evaluation criteria of the study may have led to an increase in false-positive results. Still, they also helped to evaluate the close relationship between immune profiles and OSAHS thoroughly.

CONCLUSION

In conclusion, our extensive bi-directional MR analyses revealed a causal relationship between various immune phenotypes and OSAHS, elucidating the intricate relationship between OSAHS and the immune system. In addition, our study effectively minimizes the effects of reversed causality, other variables, and unavoidable confounders, providing a new perspective for researchers to explore the biological foundations of OSAHS and potentially establishment of early prevention and treatment strategies. These discoveries widen the scope of research in psychoimmunology and provide valuable insights into the prevention of OSAHS.

ARTICLE HIGHLIGHTS

Research background

Despite being one of the most prevalent sleep disorders, obstructive sleep apnea hypoventilation syndrome (OSAHS) has limited information on its immunologic foundation. The immunological underpinnings of certain major psychiatric diseases have been uncovered in recent years thanks to the extensive use of genome-wide association studies (GWAS) and genotyping techniques using high-density genetic markers (*e.g.*, SNPs or CNVs). But this tactic hasn't yet been applied to OSAHS. Using a Mendelian randomization analysis, we analyzed the causal link between immune cells and the illness in order to comprehend the immunological bases of OSAHS.

Research motivation

In summary, our comprehensive bidirectional mendelian randomization (MR) analysis has revealed causal links between various immunophenotypes and OSAHS, shedding light on the intricate web of relationships between OSAHS and the immune system. Moreover, Reverse causality, other variables, and other unavoidable confounding factors have all been successfully reduced in impact by our study, offering a fresh perspective for researchers to delve into the biological underpinnings of OSAHS and potentially pave the way for early intervention and treatment strategies. These findings expand the realm of psychoimmunology and offer valuable insights for OSAHS prevention.

Research objectives

This study employed two-sample Mendelian randomization analysis using data from a large genomic research cohort of approximately 372657 individuals, assuring great statistical efficiency. The outcomes of the study were based on genetic instrumental variables, and causal inferences were conducted by various robust Mendelian randomization analysis techniques, which were unaffected by horizontal pleiotropy and other variables. This study does have several drawbacks, though. First, a thorough evaluation of horizontal pleiotropy is still difficult to achieve, even after several sensitivity studies. Second, stratified population analyses were not feasible due to the lack of individual-level data. Third, the study's reliance on European databases limits the generalizability of the findings to other ethnic groups. Finally, the study's flexible outcome assessment criteria may have led to more false positives, but they also made it easier to evaluate the full extent of the strong relationship between immunological traits and OSAHS.

Research methods

A comprehensive two-sample MR study was conducted to investigate the causal relationship between immune cell characteristics and OSAHS. Summary statistics for each immune cell feature were obtained from the GWAS catalog. Information on 731 immune cell properties, such as morphologic parameters, median fluorescence intensity, absolute cellular, and relative cellular, was compiled using publicly available genetic databases. The results' robustness, heterogeneity, and horizontal pleiotropy were confirmed using extensive sensitivity examination.

Research results

After false discovery rate correction, OSAHS had no statistically significant effect on immunophenotypes. However, Two lymphocyte subsets were identified to be significantly associated with OSAHS risk: (OR = 1.03, 95%CI = 1.01-1.03, $P = 0.000$); CD28+CD4+T cell (OR = 1.04, 95%CI = 1.02-1.04, $P = 0.019$).

Research conclusions

The study has shown the close association between immune cells and OSAHS through genetic methods, thereby offering direction for future clinical research.

Research perspectives

This groundbreaking study employs bidirectional MR analysis to unveil crucial immunological links in OSAHS. By establishing causal relationships between diverse immunophenotypes and OSAHS, the research offers a fresh lens for exploring the disorder's biological foundations. Successfully addressing confounding factors, the study presents opportunities for early intervention and insights into targeted preventive strategies. While limitations exist, including challenges in evaluating horizontal pleiotropy and generalizability, identifying specific lymphocyte subsets strengthens the convergence of immunology and OSAHS research, guiding future clinical investigations with promising avenues for intervention.

FOOTNOTES

Author contributions: Zhao HH assisted with planning, directing, and writing, as well as with editing and revising; Ma Z helped with the first draft of the writing, the formal analysis, and the data collection; Guan DS helped with the statistical analysis; the essay was written by all writers, who also gave their approval to the final draft.

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Institutional review board statement: The selected GWAS data is obtained from open-source databases, specifically the NHGRI-EBI Catalog (<https://www.ebi.ac.uk/gwas/>). As it originates from such sources, there is no "Institutional Review Board statement" associated with it.

Informed consent statement: Consent was not needed as the study was retrospective without exposure to the patients' data.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: Participants gave informed consent for data sharing.

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